W. West Allen (Nev. Bar No. 5566)
HOWARD & HOWARD ATTORNEYS PLLC
3800 Howard Hughes Parkway, Suite 1000
Las Vegas, NV 89169
Tel: (702) 257-1483
Email: wwa@h2law.com

Charles B. Klein (admitted *pro hac vice*)
Claire A. Fundakowski (admitted *pro hac vice*)
WINSTON & STRAWN LLP
1700 K Street N.W.
Washington, D.C. 20006
Tel: (202) 282-5000
Email: cklein@winston.com,
cfundakowski@winston.com

George C. Lombardi (admitted *pro hac vice*)
Alison A. Heydorn (admitted *pro hac vice*)
WINSTON & STRAWN LLP
35 W. Wacker Drive
Chicago, IL 60601
Tel: (312) 558-5969
Email: glombard@winston.com
aheydorn@winston.com

Eimeric Reig-Plessis (admitted *pro hac vice*)
WINSTON & STRAWN LLP
101 California Street
San Francisco, CA 94111
Tel: (415) 591-6808
Email: ereigplessis@winston.com

Attorneys for Defendants Hikma Pharmaceuticals USA Inc. and Hikma Pharmaceuticals International Limited

Michael D. Rounds (Nev. Bar No. 4734)
Ryan J. Cudnik (Nev. Bar No. 12948)
BROWNSTEIN HYATT FARBER SCHRECK, LLP
5371 Kietzke Lane
Reno, NV 89511
Tel.: (775) 324-4100 / Fax: (775) 333-8171
Email: mrounds@bhfs.com,
rcudnik@bhfs.com

Constance S. Huttner (admitted *pro hac vice*)
Frank D. Rodriguez (admitted *pro hac vice*)
James Barabas (admitted *pro hac vice*)
Caroline Sun (admitted *pro hac vice*)
Beth Finkelstein (admitted *pro hac vice*)
WINDELS MARX LANE & MITTENDORF, LLP
1 Giralda Farms, Suite 100
Madison, NJ 07940
Tel: (973) 966-3200 / Fax: (973) 966-3250
Email: chuttner@windelsmarx.com,
frodriguez@windelsmarx.com
jbarabas@windelsmarx.com,
csun@windelsmarx.com,
bfinkelstein@windelsmarx.com

Attorneys for Defendants Dr. Reddy's Laboratories, Inc. and Dr. Reddy's Laboratories, Ltd.

UNITED STATES DISTRICT COURT

DISTRICT OF NEVADA

AMARIN PHARMA, INC., et al., Plaintiffs, v. HIKMA PHARMACEUTICALS USA, INC., et al., Defendants.	Case No. 2:16-cv-02525-MMD-NJK (Consolidated with Case No. 2:16-cv-02562-MMD-NJK) **DEFENDANTS' POST-TRIAL BRIEF**

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GLOSSARY OF ABBREVIATIONS

Amarin	Plaintiffs Amarin Pharma, Inc. and Amarin Pharmaceuticals Ireland Limited
ANDA	abbreviated new drug application
Apo B	apolipoprotein B
Defs.	Defendants
DHA	docosahexaenoic acid
Dep.	Deposition transcript
DX	Defendants' trial exhibit
EPA	eicosapentaenoic acid, which is also called icosapent, icosapent ethyl, ethyl icosapentate, or "EPA-E" (i.e., ethyl EPA)
FDA	U.S. Food and Drug Administration
FFCL	Post-trial, proposed findings of fact and conclusions of law
g	gram
LDL-C	low-density lipoprotein cholesterol
mg/dL	milligrams per deciliter
PDR	Physicians' Desk Reference (a published compilation of drug labels)
Pls.	Plaintiffs
PDX	Plaintiffs' demonstrative exhibit
PX	Plaintiffs' trial exhibit
TG	triglycerides
Tr.	Trial transcript

I. INTRODUCTION

For more than seven-and-a-half years, Amarin has enjoyed a monopoly in the United States on purified EPA—a natural component of fish oil—as a treatment for severe hypertriglyceridemia. But it is undisputed that Amarin did not invent purified EPA, or its use to reduce triglycerides. For the last 30 years, a Japanese product called Epadel that is materially identical to Amarin's Vascepa® has been used to reduce triglycerides and cardiovascular risk. As a result, Amarin was unable to patent EPA itself, or its more general use to reduce triglycerides. Amarin settled instead for what the Patent Office called "a very narrow and specific method" of treatment. DX 1591 at 8-9. In asserting 10 claims on that "narrow and specific" method against Defendants, Amarin asks the Court to extend its monopoly on EPA by another decade, depriving the public of generic alternatives to Vascepa. Amarin's request should fail for four independent reasons—any one of which is sufficient, standing alone, to enter judgment for Defendants.

First, Amarin failed to prove that Defendants induce infringement of any asserted claim. As the Court previously found, Defendants' drug labels do not "explicitly tell doctors they should prescribe the drug for at least 12 weeks," as required by all asserted claims. ECF No. 278 at 9. Amarin survived summary judgment only by alleging that "doctors would understand the labelling as *requiring* treatment for more than 12 weeks" because "severe hypertriglyceridemia is *a chronic condition requiring indefinite treatment*." *Id*. at 9-10 (emphasis added). But Amarin's clinical infringement expert, Dr. Budoff, abandoned this theory at trial—admitting that severe hypertriglyceridemia is "not always a chronic condition," can "be an acute phenomenon," and for "many patients . . . do[es]n't require any drug therapy at all." Budoff Tr. 449:1-450:15, 489:23-25.

As the Court recognized in its Rule 52(c) Order, Dr. Budoff instead advanced a new theory that "the labeling instructs doctors to encourage patients to change their diet and get more exercise before [i]nitiating drug therapy," thus "*requir*[*ing*] elimination of acute causes before initiating Vascepa." Tr. 621:15-622:17 (emphasis added). Following the Court's ruling, however, Amarin's regulatory expert, Dr. Peck, admitted that the labelling does not even "suggest" (much less "require") "that Vascepa should be withheld until a patient has successfully effected a change in diet." Peck Tr. 1376:2-14. Indeed, although noting vaguely that "patients should engage in appropriate nutritional

intake and physical activity" for some unknown duration "before receiving Vascepa," the label only *instructs* and *requires* physicians to "[a]ssess lipid levels before initiating therapy." DX 2256 at 2.

Moreover, even if the label could be read to suggest to doctors to eliminate patients whose triglycerides fall below 500 mg/dL as a result of some "nutritional intake and physical activity" (it does not), Amarin's own MARINE study shows that this would not limit the use of EPA to patients who require the drug long-term. Specifically, Amarin does not dispute that "Vascepa is indicated for those patients who qualified for the MARINE trial," and that "Defendants' labels" are "directed to this patient population." Budoff Tr. 493:10-15. The MARINE study undisputedly shows that approximately one-fifth of patients prescreened with diet and exercise and having triglycerides of at least 500 mg/dL can still "achieve and maintain triglyceride levels below 500" without any drug therapy—thus refuting Amarin's claim that Vascepa's target patient population necessarily has chronic forms of severe hypertriglyceridemia requiring long-term drug administration. Budoff Tr. 495:3-7. There is no dispute that these patients could have benefited from short-term EPA therapy by being "given Vascepa immediately," followed by diet and exercise to maintain levels below 500 mg/dL—when "they wouldn't even need Vascepa" anymore. Budoff Tr. 495:20-496:4. As a result, the evidence showed that the "use of icosapent in defendants' labels is not limited to chronic use" of at least 12 weeks. Peck Tr. 1361:8-10. Instead, the labels "leave it entirely up to the physician's discretion to determine the duration of treatment." Budoff Tr. 444:8-11.

Second, the evidence is clear and convincing that all 10 asserted claims are invalid as obvious. In addition to treating a patient with severe hypertriglyceridemia for 12 weeks, all claims require a 4 g/day dose of 96% pure EPA. Multiple prior-art studies disclosed a 4 g/day dose of 96% pure EPA—including Mori, which also expressly taught that LDL-C is "not affected significantly by EPA." DX 1538 at 1. Amarin's validity expert, Dr. Toth, admitted that "a skilled artisan would have been motivated to avoid LDL-C increases when treating patients with severe hypertriglyceridemia" (Toth Tr. 1822:8-11), so there should be no dispute that Mori's purified EPA was at least obvious to try.

Amarin's contrary argument rests on the premise that a skilled artisan would believe the exact opposite of what the prior art expressly disclosed. According to Amarin, a skilled artisan would disregard prior art specific to EPA like Mori, and instead focus on the effects of *unrelated compounds*

(e.g., fibrates) at triglyceride levels *far above* 500 mg/dL. Pls.' FFCL ¶¶ 707-08. No prior art supports Amarin's contrived argument, which contradicts its own contemporaneous representations.

Just months after the alleged invention date, Amarin assured its regulator (FDA) that "[i]n clinical studies performed with Ethyl-EPA . . . there is *no evidence* of a significant rise in LDL-[C]." DX 1816 at 85 (emphasis added). Likewise, citing only the prior art available to the public, Amarin assured its investors that "Multiple Studies *Demonstrate* that EPA is LDL Neutral." DX 1800 at 13 (emphasis added). As Amarin's witnesses confirmed, these statements were "accurate," "truthful," and did not "mischaracteriz[e] the prior art." Ketchum Tr. 211:5-15; Toth Tr. 1834:13-16.

Indeed, third-party prior-art studies—not any of Amarin's own findings—were the only basis for Amarin's patent filings, which contain "no data." Toth Tr. 1800:14-18. Dr. Toth could not even articulate what Amarin purportedly invented—he could only speculate that "sure[ly] they had something." Toth Tr. 1800:19-1801:11. In fact, what "they had" was repackaging what was available in the public domain. Because the "patent[s] set[] forth no human clinical or laboratory data showing" that EPA reduces triglycerides without raising LDL-C, it would be "clearly err[oneous] [to] find[] any difference between the claimed invention and the [prior art] on this point." *Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1374 (Fed. Cir. 2005) (reversing judgment of nonobviousness).

While Amarin eventually conducted confirmatory clinical studies, MARINE and REDUCE-IT, years *after* its patent filings, the statutory reward for those efforts is not patent protection—it is FDA regulatory exclusivity, which Amarin received. *E.g.*, 21 U.S.C. § 355(j)(5)(F)(ii), (iii). Regardless of how well designed, conducted, or praised Amarin's clinical studies may be, they do not warrant a 20-year patent monopoly for patents filed many years before the studies were even conducted. Thus, not only did Amarin apply for patents based exclusively on the prior art, its later "[s]cientific confirmation of what was already believed to be true may be a valuable contribution, but it does not give rise to a patentable invention." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1363-64 (Fed. Cir. 2007) (reversing jury verdict of nonobviousness).

Third, at a minimum, Defendants do not infringe the three claims that exclude "concurrent lipid altering therapy," and the remaining seven claims (which are broad enough to include the combination of EPA with a statin to reduce LDL-C and Apo B) were at least obvious to try.

Nothing in Defendants' labels even resembles an instruction to exclude concurrent lipid altering therapy. At best, the labels are agnostic to the concurrent administration of a lipid altering therapy. The single sentence in the clinical studies section that Amarin relies on—"[t]wenty-five percent of patients were on concomitant *statin* therapy"—which Amarin interprets to mean "that the remaining 75% of patients . . . were not on *concurrent lipid altering* therapy," does not support its position. Pls.' FFCL ¶¶ 352-53 (emphasis added). Amarin's argument makes a logical leap—and, regardless, this statement is not an instruction. As Dr. Budoff admitted, "there are other lipid-altering therapies" besides statins, so the cited statement "doesn't say anything about whether this 75 percent of patients were taking a different lipid-altering therapy." Budoff Tr. 520:13-25, 522:19-25.

As to obviousness, there is no dispute that the remaining seven claims include the use of a statin, which was obvious to combine with EPA to achieve all of the claimed effects. As Dr. Toth admitted, "it was known that EPA could be used with a statin" and that "statins can reduce LDL-C and apo B," regardless of "whether the triglyceride level is 400 or 550." Toth Tr. 1876:25-1877:2, 1876:13-15, 1880:1-3. That combination, which was known in the art, falls within the scope of all "claims that allow for the use of a statin[,] [which] would include using 4 grams pure icosapent with a statin to . . . not have an LDL-C increase," as well as "to reduce apo B." Toth Tr. 1886:15-24.

Fourth, Defendants do not infringe the nine claims that require specific effects on lipid levels. Amarin relies exclusively on median data and a summary in the clinical studies section, but "these are not instructions." Budoff Tr. 511:9-15. And Vascepa is not FDA-approved to achieve any of the claimed effects on lipid levels. At bottom, Amarin's theory is that a doctor would compare the reported data to "the prescribing information for Lovaza," which "warn[s] about LDL rise," and be encouraged to administer Defendants' products instead of Lovaza because Defendants' labels do not include such a warning. Pls.' FFCL ¶ 330. But that theory violates Federal Circuit precedent, which bars "look[ing] outside the label to understand the alleged implicit encouragement in the label." *Takeda Pharm. U.S.A., Inc. v. W.-Ward Pharm. Corp.*, 785 F.3d 625, 634 (Fed. Cir. 2015).

The remaining, broadest claim—'929 patent claim 1—merely requires "reducing triglycerides in a subject having fasting triglycerides of at least 500 mg/dl," regardless of any effects on LDL-C or Apo B. That result was undisputedly obvious: As Dr. Toth admitted, a skilled artisan "would have

reasonably expected purified EPA to reduce triglyceride levels above 500." Toth Tr. 1860:12-15.

Each of these independent grounds to enter judgment for Defendants is explained in greater depth below, and in Defendants' proposed findings of fact and conclusions of law (ECF No. 373).

II. ARGUMENT

A. Amarin failed to prove that Defendants' labels satisfy the 12-week limitation.

1. Amarin bears the burden of proving an infringing instruction.

As the Court recognized on summary judgment, "the question of whether Defendants may be held liable for inducing infringement" turns on "'whether the proposed label *instructs* users to perform the patented method.'" ECF No. 278 at 7 (quoting *Grunenthal GMBH v. Alkem Labs. Ltd.*, 919 F.3d 1333, 1339 (Fed. Cir. 2019) (emphasis added)). The legal requirement for an "instruct[ion]" is especially critical here because, as the Court found, "reducing triglycerides in less than 12 weeks using Defendants' ANDA drugs is a substantial non-infringing use." *Id*. at 12-13. Where, as here, a "product has substantial noninfringing uses, intent to induce infringement cannot be inferred." *HZNP Meds. LLC v. Actavis Labs. UT, Inc.*, 940 F.3d 680, 702 (Fed. Cir. 2019) ("*Horizon*") (quotation omitted). Thus, inducement cannot be found based on instructions that are merely *inferred*. That "some users might infringe" after reading the label, for example, "does not establish that the proposed label instructs users to perform the patented method." *Id*. (quotation omitted).[1]

The cases that Amarin relies on reinforce this principle. In its proposed findings, Amarin repeatedly cites *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1369 (Fed. Cir. 2017), for the proposition that Amarin only needs to prove that "some physicians" reading the label will "inevitably" infringe. Pls.' FFCL ¶¶ 281, 293, 297. In *Eli Lilly*, however, "the product labeling include[d] repeated instructions," and "[t]he instructions [we]re unambiguous on their face and encourage[d] or recommend[ed] infringement." 845 F.3d at 1369. The same was true in *Vanda Pharm. Inc. v. W.-Ward Pharm. Int'l Ltd.*, 887 F.3d 1117 (Fed. Cir. 2018), which Amarin also cites. Pls.' FFCL ¶¶ 293, 297. The Federal Circuit there relied on "clear recommendations" that

[1] Amarin mischaracterizes Defendants' argument as "assert[ing] that the existence of a substantial noninfringing use for a proposed product precludes a finding of induced infringement." Pls.' FFCL ¶ 294. That is a straw man. As we made clear at trial, our argument is that inducement cannot be *implied*; there must be an *instruction* in the label to infringe. Opening Tr. 37:12-19.

"instruct[ed] . . . the patented method." 887 F.3d at 1132. The Federal Circuit did not need to "infer intent to induce infringement," because "the proposed label itself recommend[ed] infringing acts." *Id*. at 1133 (quotation omitted). Amarin's own cases thus confirm that inducement here cannot be inferred, but requires a clear instruction in the label itself. Defs.' FFCL ¶¶ 595-600.

Without instructions to infringe, Amarin's inducement case fails—regardless of how many doctors ultimately infringe. "Speculation or even proof that some, or even many, doctors would prescribe [a drug in an infringing way] is hardly evidence of inevitability." *Takeda*, 785 F.3d at 633. This is true even if "less than 5%" of uses are noninfringing, and 95% infringe. *In re Depomed Pat. Litig.*, 2016 WL 7163647, at *69 (D.N.J. Sept. 30, 2016), *aff'd*, *Grunenthal*, 919 F.3d 1333.[2]

Amarin's attempt to *imply* inducement without specific instructions is contrary to precedent. As Dr. Budoff admitted, Amarin's theory "really is" that the labelling "will [*im*]*ply* to doctors that they should go ahead and use the drug for at least 12 weeks." Budoff Tr. 445:23-446:2 (emphasis added). But inducement "cannot be inferred." *Horizon*, 940 F.3d at 702. Nor can Amarin rely on Dr. Sheinberg's answer that "anything is possible" when asked if it is "possible that some physicians could read the label . . . and be induced to infringe." Sheinberg Tr. 655:7-656:2; Pls.' FFCL ¶ 282. Such "possible infringement" by some physicians is not sufficient for "specific intent and action to induce infringement[,] [which] must be proven." *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1364 (Fed. Cir. 2003). Nor could possible inducement satisfy Amarin's burden by "a preponderance of the evidence," requiring "that the existence of a fact is more *probable* than its nonexistence." *Ortiz v. Principi*, 274 F.3d 1361, 1365 (Fed. Cir. 2001) (emphasis added). Regardless of what hypothetically may be "possible," there is no "actual instruction directed to any physicians in the label to administer defendants' products for at least 12 weeks." Sheinberg Tr. 703:21-704:2.

Amarin emphasizes that "VASCEPA is—and Defendants' ANDA Products by extension will be—approved for chronic administration." Pls.' FFCL ¶ 319. But while there is no dispute that EPA is *approved* for chronic use (*id*. ¶ 84), that does not mean the labelling here is limited to chronic use

[2] Amarin notes that in *Sanofi v. Watson Labs. Inc.*, "77% of the prescriptions were for an infringing use, leaving 23% of the prescriptions directed to noninfringing uses." Pls.' FFCL ¶ 295 (citing 875 F.3d 636, 645 (Fed. Cir. 2017)). But the inducement finding was "based on interpreting the label's express statement[s]," not simply that infringement was common. 875 F.3d at 646.

or *instructs* such use. Indeed, in both *Grunenthal* and *Horizon*, the Federal Circuit held that drug labels did *not* instruct uses that were undisputedly within the scope of FDA approval.

In *Grunenthal*, the drug was indicated to treat "severe chronic pain," which included the patented use to treat "polyneuropathic pain." 919 F.3d at 1339. The patentee argued that the indication would inevitably lead at least some doctors to infringe. But the Federal Circuit rejected that theory, holding that "even if severe chronic pain includes polyneuropathic pain, it also includes [other kinds of severe chronic] pain. Therefore, the proposed ANDA labels do not *specifically encourage* use of [the drug] for treatment of polyneuropathic pain." *Id*. (emphasis added).

Similarly, the patented method in *Horizon* required a user to "(1) apply the inventive formulation, (2) wait for the area to dry, and (3) apply sunscreen, insect repellant, or a second topical medication." 940 F.3d at 702. The label described each of these steps, instructing users to "wait until the treated area is dry before applying a second topical agent." *Id*. at 686 (quotation and alteration omitted). Yet the Federal Circuit found no inducement: While "[t]he patented method here *requires* three distinct steps," the label "only *require*[*s*] the first step of this method." *Id*. at 702 (emphasis added). Because "the label does not *require* subsequent application" of another drug, as required by the asserted claims, the label "does not encourage infringement." *Id*. (emphasis added).

This case is analogous to *Grunenthal* and *Horizon*. While the scope of FDA approval includes chronic use, it also includes uses for less than 12 weeks that do not infringe. As Dr. Budoff admitted, the labels "leave it entirely up to the physician's discretion to determine the duration of treatment," and "it would be entirely consistent with defendants' labels for a doctor to prescribe icosapent for less than 12 weeks." Budoff Tr. 444:8-11, 445:5-8. Likewise, Dr. Peck agreed that "there's no statement anywhere in defendants' labels requiring doctors to use icosapent for at least 12 weeks," and "no minimum or maximum therapy duration." Peck Tr. 1390:1-4, 1389:12-14. Thus, "a doctor could even prescribe icosapent for only three weeks and it would not be inconsistent with the label." Peck Tr. 1403:11-14. The label does not "specifically encourage" or "require" the patented method.

2. Defendants' labels as a whole do not instruct 12-week therapy.

While admitting that the labelling leaves the duration of therapy to the doctor's discretion, Amarin points to three sections of the labelling, arguing that they induce doctors to administer EPA

for at least 12 weeks. Pls.' FFCL ¶¶ 298-313. These arguments fail. Defs.' FFCL ¶¶ 572-91.

a. The indication section does not require 12-week therapy.

As the Court found in its summary judgment ruling, "the indications and usage section . . . does not specify a duration of treatment." ECF No. 278 at 9. The Court's ruling left a narrow window to show inducement: Amarin had to prove that "doctors would understand the labelling as *requiring* treatment for more than 12 weeks" because "doctors know severe hypertriglyceridemia is a chronic condition *requiring* indefinite treatment." *Id*. at 9-10 (emphasis added). In other words, Amarin needed to prove that the indication for treating "severe hypertriglyceridemia" refers to a condition that is necessarily chronic and requires long-term drug therapy. Absent such proof, the mere fact that the indicated use for treating severe hypertriglyceridemia "includes" chronic use, without "specifically encourag[ing]" it, is insufficient as a matter of law. *Grunenthal*, 919 F.3d at 1339. Based on Amarin's own expert testimony, Amarin was unable to meet its burden.

As Dr. Budoff admitted, severe hypertriglyceridemia is "not always a chronic condition"—it has "reversible causes" and "can be an acute phenomenon." Budoff Tr. 449:1-13, 450:12-15. Indeed, FDA rejected Amarin's attempt to characterize Vascepa patients as a "chronic care population" in the label. Defs.' FFCL ¶¶ 93-94; *compare* DX 2247 at 4 *with* DX 2248 at 4. Dr. Budoff also admitted that "severe hypertriglyceridemia does not necessarily require indefinite drug therapy," and "many patients . . . don't require any drug therapy at all." Budoff Tr. 489:19-25; *see also* Defs.' FFCL ¶¶ 86-118. In short, "the indicated use of icosapent in defendants' labels is not limited to chronic use." Peck Tr. 1361:8-11. Amarin's four post-trial arguments are unpersuasive. ECF No. 278 at 9.

First, Amarin argues that the record shows that "severe hypertriglyceridemia has a strong genetic component." Pls.' FFCL ¶ 302. But that does not mean that genetics are the *sole* cause of most patients' severe hypertriglyceridemia, or that patients with genetic predispositions for *high* triglycerides will necessarily develop *very high* triglycerides. As Dr. Budoff conceded, "pure genetic disorders" are "rare," and "the cause of severe hypertriglyceridemia in most patients is not solely genetics." Budoff Tr. 463:1-5, 468:5-11. While genetics often play some role, "it's less rare for patients to have a genetic predisposition to high triglycerides, and then there are other factors that

cause them to go above 500." Budoff Tr. 463:7-11; *see also* Sheinberg Tr. 595:11-596:25.[3]

Second, Amarin cites Dr. Budoff's view that "prescribers perceive severe hypertriglyceridemia as *generally* a chronic condition requiring long-term drug therapy." Pls.' FFCL ¶ 303 (emphasis added). As Amarin admits, that view was disputed by Dr. Sheinberg, who testified that severe hypertriglyceridemia is only "sometimes" chronic, in a "lower" proportion of cases. *Id.* But even if severe hypertriglyceridemia were "generally" chronic, that would not meet Amarin's burden of proof. The indicated use in *Grunenthal* for "severe chronic pain" also "generally" resulted in infringement—the drug was used to treat noninfringing conditions "less than 5%" of the time. *In re Depomed*, 2016 WL 7163647, at *69, *aff'd*, *Grunenthal*, 919 F.3d 1333. The facts here are remarkably similar: "about 5 percent of [Dr. Budoff's own] patients with severe hypertriglyceridemia take Vascepa for less than 12 weeks." Budoff Tr. 501:11-14. Thus, while the indicated use for treating severe hypertriglyceridemia "includes" patients who require EPA for longer than 12 weeks, "it also includes" patients who can take the drug for less time (even if that is only 5% of patients), so the labelling "do[es] not specifically encourage" long-term use. *Grunenthal*, 919 F.3d at 1339.

Third, while admitting that lifestyle changes alone can reduce triglycerides, Amarin argues that they take longer than 12 weeks to take effect. Pls.' FFCL ¶ 304. Amarin alleges that "Dr. Fisher conceded" that "it takes 6 months for lifestyle changes to effect a reduction in body mass sufficient for them to stop their medication." *Id.* But that "conc[ession]" (*id.*) was limited to how long it takes patients "to lose enough weight" to reduce triglycerides—it did not relate to other lifestyle modifications that take effect more quickly. Fisher Tr. 1175:2-10. For example, Amarin's own researchers concluded that "diets are remarkable in how quickly they lower serum TGs," which "is independent of the effect of diet on adiposity" (i.e., weight-loss effects). PX 833 (Friedewald 2013) at 4; *see also* Sheinberg Tr. 704:3-21 (discussing lifestyle modifications besides weight loss).

Fourth, Amarin cites "real-world evidence" that Drs. Budoff and Sheinberg prescribe Vascepa long-term. Pls.' FFCL ¶ 305. But "proof that some, or even many, doctors [infringe] is hardly

[3] Amarin contends that "genetic impairments relating to lipoprotein lipase [are] a primary cause of severe hypertriglyceridemia." Pls.' FFCL ¶ 23; *see also id.* ¶ 43. But patients with "lipoprotein lipase impairment or deficiency" were "excluded" from the MARINE study, on which Vascepa's indication for severe hypertriglyceridemia is based. Toth Tr. 1890:2-16; DX 1694 at 32.

evidence of" inducement, *Takeda*, 785 F.3d at 633, and whether doctors infringe "without inducement . . . is legally irrelevant." *Warner-Lambert*, 316 F.3d at 1364. In any event, "85 percent" of Dr. Budoff's Vascepa prescriptions are for uses other than treating severe hypertriglyceridemia (e.g., reducing cardiovascular risk), so his prescribing practices do not bear on the indicated use of Defendants' products. Budoff Tr. 506:5-509:9; *see also* Sheinberg Tr. 590:20-591:12.

b. The dosage section does not require 12-week therapy.

Lacking support for its original infringement theory, Amarin presented a new theory at trial that was not in its summary judgment brief, or any of its pretrial filings. This new theory relies on two bullets in section 2.1 of the dosage and administration section, which according to Amarin "instructs physicians to address transient causes first and encourages use of the drug solely in chronic cases resistant to lifestyle changes." Pls.' FFCL ¶ 308. As with Amarin's original theory, however, this new theory was contradicted at trial by Amarin's own experts. Defs.' FFCL ¶¶ 592-622.

The first bullet in section 2.1 simply tells doctors to "[i]dentify" certain causes "of high triglyceride levels and manage as appropriate." DX 2256 at 2. As Dr. Budoff admitted, this statement "leaves it up to the discretion of the doctor to manage as the doctor feels is appropriate." Budoff Tr. 470:7-10. It "is not telling doctors don't give icosapent yet, address those other factors first," and "certainly isn't saying only give icosapent if absolutely necessary and the only causes are genetics." Budoff Tr. 470:11-18; *see also* Sheinberg Tr. 605:7-16; Defs.' FFCL ¶¶ 149-58.

As for the second bullet, it merely states that "[p]atients should engage in appropriate nutritional intake and physical activity before receiving" EPA. DX 2256 at 2. As Dr. Peck admitted, this "does not limit the patient population for whom Vascepa is approved based on prior diet," and "does not suggest that Vascepa should be withheld until a patient has successfully effected a change in diet." Peck Tr. 1367:16-18, 1376:2-14. In particular, the label "does not require doctors to wait and see if patients fail to maintain triglycerides below 500 [mg/dL] with diet and exercise," and "does not suggest . . . that the drug should not be used . . . unless a patient has been placed successfully on a diet for a specific amount of time." Peck Tr. 1381:13-1382:25. "If FDA had intended to limit Vascepa's approval to patients who previously consumed a particular diet [for a specific amount of

time], it would have so stated in the Indications and Usage section." Peck Tr. 1373:2-8.[4]

Even if the label implicitly instructed doctors to first try diet and exercise for some period of time, Amarin's own MARINE study shows that such an instruction would not inevitably lead doctors to treat patients for at least 12 weeks. In MARINE, all patients were treated with diet and exercise for up to nine weeks before the 12-week trial began. Defs.' FFCL ¶ 123. At that point, patients were divided into Vascepa-treated groups and a placebo group, which continued diet and exercise alone. *Id.* ¶ 127. If Amarin were correct that diet and exercise eliminates patients with "transient" causes of severe hypertriglyceridemia, all patients who qualified for MARINE would require chronic drug therapy to reduce their triglycerides below 500 mg/dL. But in reality, 21% of patients in the placebo arm were able to reduce their triglycerides below 500 mg/dL without any drug therapy, simply by continuing diet and exercise. *Id.* ¶¶ 132-34; DX 1701 at 51. Thus, 21% of patients in MARINE could have benefited from short-term EPA therapy by being "given Vascepa immediately," followed by diet and exercise to maintain levels below 500 mg/dL—when "they wouldn't even need Vascepa" anymore. Budoff Tr. 495:20-496:4; *see also* Sheinberg Tr. 635:11-638:20.

c. The clinical studies section does not require 12-week therapy.

Lastly, Amarin relies on the clinical studies section. Pls.' FFCL ¶¶ 309-13. But as the Court previously found, this section merely "*describes* a clinical trial (the 'MARINE Trial') in which patients were enrolled for 12 weeks"; it does not "*explicitly tell* doctors they should prescribe the drug for at least 12 weeks." ECF No. 278 at 9 (emphasis added). As a matter of law, this is not enough: "*Merely describing* the infringing use . . . *will not suffice*; specific intent and action to induce infringement must be shown." *Horizon*, 940 F.3d at 702 (emphasis added); Defs.' FFCL ¶¶ 623-32.

Amarin argues that the clinical studies section encourages 12-week use because it reports "only the effects on the patients' TGs and other lipid levels after 12 weeks of administration; no data for other time frames is available." Pls.' FFCL ¶ 311. But as Dr. Peck admitted, "you can't

[4] There is also no specified time period during which patients should "engage in appropriate nutritional intake . . . before receiving" EPA. DX 2256 at 2. Thus, section 2.1 "does not prevent physicians from, consistent with established clinical practice, discussing diet changes and prescribing Vascepa in the same visit." Peck Tr. 1380:23-1381:2. This comports with the clinical reality that "engag[ing] in appropriate nutritional intake" often involves *refraining* from certain foods and drinks (e.g., sugars and alcohol), which begins immediately. Sheinberg Tr. 608:21-609:10.

reasonably read [the clinical studies section] as saying, okay, the study was 12 weeks, therefore doctors should prescribe the drug for 12 weeks, no less, no more." Peck Tr. 1406:6-10. At most, "the labeling is telling doctors that they *can* use the drug for 12 weeks or longer if they want, but it's not saying that they *should*." Peck Tr. 1397:1-6 (emphasis added). Likewise, Dr. Budoff agreed that "defendants' labels don't . . . say[] because these effects were achieved in 12 weeks, make sure you give the drug for at least 12 weeks." Budoff Tr. 504:9-13. Nor would a doctor necessarily expect the described effects to occur—in 12 weeks or otherwise—because "median data from a clinical trial may or may not relate to an individual patient." Budoff Tr. 512:6-9; Defs.' FFCL ¶¶ 160-66.

Amarin cites *Sanofi v. Glenmark Pharm. Inc., USA*, 204 F. Supp. 3d 665 (D. Del. 2016), as a "remarkably similar" case that found induced infringement where "the label reported a clinical trial and the length of that trial would further encourage clinicians to administer for at least the claimed duration of 12 months." Pls.' FFCL ¶ 312. But in that case, unlike here, "the indications and usage section . . . direct[ed] a physician to look at the clinical studies section" with express "instructions" to do so. 204 F. Supp. 3d at 679, 678. *Sanofi* is thus inapposite and does not support inducement.[5]

B. All asserted claims are invalid for obviousness.

As a second, independent basis to rule for Defendants, all 10 claims are invalid as obvious.

1. The prior art rendered the asserted claims at least obvious to try.

"One of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 419-20 (2007). As articulated by Dr. Heinecke at trial (*e.g.*, Tr. 759:10-760:1), that is the case here:

- The Lovaza PDR (DX 1535) taught a method of treating patients with triglycerides of at least 500 mg/dL by administering, for at least 12 weeks, a 4 g/day dose of a mixture of EPA and DHA. This method, however, often raised patients' LDL-C levels.
- Consistent with other prior-art studies, Mori (DX 1538) taught that DHA raised LDL-C, whereas 4 g/day of 96% pure EPA reduced triglycerides without raising LDL-C.
- Thus, to avoid an increase in LDL-C, it was obvious to substitute Mori's 4 g/day dose of 96% pure EPA for the mixture of EPA and DHA used in the Lovaza indication.

[5] The district court's holding in *Sanofi* regarding the duration of treatment (which preceded both *Grunenthal* and *Horizon*) was not appealed, and thus was never considered by the Federal Circuit.

The motivation to solve the problem of Lovaza's LDL-C side effect was undisputed at trial. As Dr. Toth admitted, "a skilled artisan would have been motivated to avoid LDL-C increases when treating patients with severe hypertriglyceridemia." Toth Tr. 1822:8-11. Dr. Toth also did not dispute that "a skilled artisan seeing that there's DHA and EPA in Lovaza, and seeing a side effect, would at least consider whether the side effect could be associated with only DHA or only EPA." Toth Tr. 1787:6-10. Nor did he dispute that "Mori found that the increase of LDL-C with DHA was statistically significant and the increase with EPA was not." Toth Tr. 1788:18-25.

At a minimum, this method was "obvious to try" because there was "a design need or market pressure to solve a problem"—i.e., the increase in LDL-C with Lovaza—and "a finite number of identified, predictable solutions" including pure EPA. *KSR*, 550 U.S. at 421. As Dr. Toth admitted, "purified EPA, such as Epadel, was given to patients before March 2008 to reduce triglyceride levels," and a skilled artisan "would have found it obvious to use either pure DHA, or pure EPA." Toth Tr. 1823:18-1824:6; *see also* Heinecke Tr. 760:2-761:5. Given Lovaza's two active ingredients, "[t]he prior art would have funneled the formulator toward these two options; he would not have been required to try all possibilities in a field unreduced by the prior art." *Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1350 (Fed. Cir. 2009). Indeed, treating severe hypertriglyceridemia with pure EPA had *already* been tried—four prior-art studies on EPA had "at least one patient . . . with triglycerides above 500." Toth Tr. 1862:23-1863:1. Likewise, there was "a finite number of available doses for pure EPA," and "at least six prior art references . . . disclosed the use of 4 grams per day of purified EPA." Toth Tr. 1858:4-19, 1855:20-25; Defs.' FFCL ¶¶ 653-63.[6]

In addition to the claimed method, all but one asserted claim requires certain lipid effects—a minimum reduction in triglycerides (e.g., about 20%), no increase in LDL-C, or a reduction in Apo B. Claim 16 of the '728 patent further requires a more specific level of EPA purity. All of these limitations were taught by the prior art: (a) Mori and Hayashi taught that EPA reduced triglycerides by at least about 20%; (b) Mori, Hayashi, and Kurabayashi taught that EPA did not increase LDL-C;

[6] That there were "potentially infinite" options is beside the point. Pls.' FFCL ¶ 721. While "the universe of potential [choices] is theoretically unlimited," the obvious-to-try inquiry turns on options "in the prior art that had clinical support." *In re Copaxone*, 906 F.3d 1013, 1026 (Fed. Cir. 2018).

(c) Kurabayashi taught that EPA reduced Apo B; and (d) WO '900 taught 99.9% pure EPA. In combination, these references rendered each asserted claim obvious. Defs.' FFCL ¶¶ 664-722. Indeed, Amarin admits that these references were "considered by the Patent Examiner during prosecution," who "concluded that the Asserted Claims were *prima facie* obvious." Pls.' FFCL ¶¶ 500, 543; DX 1591 at 9. The examiner found—correctly—that a skilled artisan would be motivated to practice the claims with a reasonable expectation of success. Toth Tr. 1804:22-1806:1.

2. Amarin's counterarguments are legally and factually flawed.

a. Amarin cannot argue that more clinical data were needed.

Despite the examiner's conclusion, Amarin argues that a skilled artisan would not have had a reasonable expectation of success because the prior art lacked data on the LDL-C effects of EPA in patients with triglycerides above 500 mg/dL. *E.g.*, Pls.' FFCL ¶¶ 550, 566, 579, 704. But as a matter of law, Amarin cannot rely on a lack of clinical data in the prior art when its *own* patents lack such data. Defs.' FFCL ¶¶ 727-39. The Federal Circuit's decision in *Merck*, 395 F.3d 1364, is instructive. There, based on a similar argument, the district court distinguished the prior art because it lacked data showing that the claimed method "overcame concerns in the art with adverse GI side effects." *Id*. at 1373. But the Federal Circuit reversed, holding that this cannot be a basis to uphold a patent where "the claimed invention adds nothing beyond the teachings" of the prior art:

> The [asserted] patent sets forth no human clinical or laboratory data showing the safety and tolerability of the treatment methods claimed by the patent. . . . So while the district court may be correct in finding the [prior-art] articles may have invited skepticism based on concerns for dose-related GI problems, *the claimed invention adds nothing beyond the teachings of those articles. Thus, the district court clearly erred in finding any difference between the claimed invention and the articles on this point*.

Id. at 1374 (emphasis added). Since *Merck*, the Federal Circuit has repeatedly applied the same principle. *See Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1369 (Fed. Cir. 2012) (reversing judgment of nonobviousness and rejecting "argu[ment] that [the prior art] would not give a skilled artisan an expectation" of clinical safety, because "neither does the [asserted] patent," which was "not based on testing in humans"); *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014) (rejecting argument that prior art lacked "antifracture efficacy" data where the "patents do not themselves present [such] data"); *In re Copaxone*, 2017 WL 401943, at *17 (D. Del. Jan. 30, 2017),

aff'd, 906 F.3d 1013 ("It would constitute clear error for the court to discredit the [prior art] for the same lack of dosing frequency clinical data from which the patents-in-suit suffer.").

Merck and its progeny are on point. Amarin's patents contain no data whatsoever, much less the clinical data that Amarin contends was missing in the prior art. Toth Tr. 1799:14-19. At least in *Merck* and *Alcon*, the patents included data from animal or *in vitro* studies. 395 F.3d at 1374; 687 F.3d at 1369. This is thus an even stronger case than *Merck* or *Alcon* to reject the argument that more data were required for a reasonable expectation of success.

Amarin cannot distinguish these cases, which it admits relied on "the absence of any real distinction between what the prior art taught and what the patents-in-suit disclosed as indicative of the absence of any real invention." Pls.' FFCL ¶ 757. Instead, Amarin contends that the specification here "provides extensive information"—i.e., predictions for "various biomarkers" and "the MARINE Clinical Study design." *Id.* ¶ 759. But under Amarin's expert's own view, that is not a substitute for data. To Dr. Toth, neither "a prediction" nor "a clinical trial protocol" could provide a reasonable expectation of success—not "until the results come out." Toth Tr. 1792:2-18. And far from providing *more* data than the prior art, Amarin's patents have *less*: Mori "contains more information about LDL neutral effects from 4 grams pure EPA than Amarin's own patents." Toth Tr. 1800:14-18.

Amarin argues that "the MARINE trial results [ ] were submitted to the Patent Office prior to allowance of the claims." Pls.' FFCL ¶ 760. But that was long after the 2009 filing date. There were no MARINE results to submit "until late 2010," and the claims were not allowed until 2012. Toth Tr. 1793:5-8; DX 1591. Nor did *Merck* look to whether data were discussed during prosecution. The problem was that the "*patent* sets forth no . . . data." 395 F.3d at 1374 (emphasis added). The patents here also set forth no data, so a lack of data in the prior art cannot be the basis for validity.[7]

[7] Amarin cites *Novartis Pharm. Corp. v. W.-Ward Pharm. Int'l Ltd.*, 287 F. Supp. 3d 505, 517 (D. Del. 2017), which distinguished *Merck* where "no prior art reference" disclosed the use of a drug to treat the claimed condition, and thus "[t]he prior art d[id] not disclose all elements of the asserted claims." *See* Pls.' FFCL ¶ 756. Here, however, the prior art disclosed all claim elements, including the use of EPA to treat severe hypertriglyceridemia. Toth Tr. 1862:23-1863:1. While Amarin cites *Novartis* as being affirmed, the Federal Circuit decision did not endorse the district court's reading of *Merck*, and in fact criticized the district court because it "erred in applying [a] heightened standard" for obviousness. 923 F.3d 1051, 1059 (Fed. Cir. 2019).

b. Amarin cannot dispute the *reasonable* expectation of success.

Amarin also points to alleged flaws in prior studies, including sample sizes and study designs. Pls.' FFCL ¶¶ 549-82. These criticisms ignore that "[c]onclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success." *Hoffmann-La Roche*, 748 F.3d at 1331. Thus, "obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) (reversing judgment of nonobviousness). "Despite certain identified shortcomings" in an obviousness combination, skilled artisans "*can* draw reasonable inferences about the likelihood of success even without a perfectly designed clinical trial." *Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, 903 F.3d 1310, 1332, 1334 (Fed. Cir. 2018).

Here, the prior art provided a reasonable expectation of success. Defs.' FFCL ¶¶ 740-50, 766-69. None of the cited studies warned that their results were limited to patients with lower triglycerides. In fact, Hayashi concluded that EPA "has no deleterious effect on plasma LDL-C" after studying patients with mean triglycerides of 300 ± 233 mg/dL, and at least one patient above 500 mg/dL. DX 1532 at 7; Lavin Dep. 102:24-103:21. At a minimum, Hayashi included patients with triglycerides of 425 and 375 mg/dL, and accurately measured LDL-C in patients below 400 mg/dL. Toth Tr. 1655:21-1656:2, 1658:23-1659:4. There was no reason to believe the results would materially change at 500 mg/dL. After all, "[t]he 500 threshold was not set because above 500 you are expected to have a greater increase in LDL-C in response to a drug," but for the unrelated reason of avoiding pancreatitis. Toth Tr. 1860:3-7, 1859:6-21. Even if LDL-C were expected to increase at materially *higher* triglyceride levels (e.g., above 700 mg/dL), the reasonable expectation of success at exactly 500 mg/dL is enough to find all claims invalid. *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1281 (Fed. Cir. 2015) ("claims which are broad enough to read on obvious subject matter are unpatentable even though they also read on nonobvious subject matter") (quotation omitted).

Amarin cannot credibly dispute that Mori and other prior art provided that reasonable expectation. Amarin itself repeatedly relied on the same prior art for the same purpose:

- Five days *before* the alleged invention date of March 25, 2008, Amarin observed that "Epadel treatment does not appear to have the same [e]ffect on LDL levels" as Lovaza, and cited Mori as showing that "[s]erum LDL increased significantly with DHA (by 8%)

but not with EPA (3.5%)." DX 1829 at 4-5, 11; DX 2241 (identifying metadata).

- In June 2008, Amarin told FDA that "[i]n clinical studies performed with Ethyl-EPA to date . . . there is no evidence of a significant rise in LDL-cholesterol." DX 1816 at 85.
- In March 2010 (still before the MARINE results), Amarin told investors that "Multiple Studies Demonstrate that DHA Raises LDL-C," and "Multiple Studies Demonstrate that EPA is LDL Neutral," citing Mori and Kurabayashi. DX 1800 at 12-13.
- In reporting the MARINE results, Amarin again cited Mori and Kurabayashi as prior-art studies showing that "although DHA treatment generally increased LDL cholesterol levels, EPA therapy did not." DX 1741 at 1, 7, 9.
- Even after Vascepa's approval, in a citizen petition to FDA, Amarin represented that "[t]he data from [Mori] support . . . that EPA and DHA have differential effects on other well-studied lipid parameters such as LDL-C." DX 2104 at 9-10.

Defs.' FFCL ¶¶ 371-97. Amarin's witnesses concede that these statements were accurate. Ketchum Tr. 210:20-211:15; Toth Tr. 1834:9-16, 1836:2-17. Amarin's efforts to avoid them now lack merit.

First, Amarin argues that its representations are irrelevant because they follow "[t]he inventor's own path." Pls.' FFCL ¶ 745. But none of these statements were made by any named inventor. At most, Amarin speculates that statements in DX 1829 could have originated from Dr. Manku because Amarin was a small company at the time. *Id*. ¶¶ 749-51. But as shown by metadata (DX 2241), the statements were made *before* Dr. Manku even allegedly conceived of the "invention."

In any event, these statements are not about Amarin's *own* studies; they merely characterize the prior art. The Federal Circuit has repeatedly relied on patentee representations to FDA and in internal documents to rebut contrary arguments about the prior art. For example, in *Copaxone*, the Federal Circuit relied on a patentee's "statement to FDA that 'one may certainly expect'" a claimed effect based on the prior art. 906 F.3d at 1029-30. While that statement itself was not "invalidating prior art," it was "evidence of a [skilled artisan]'s motivations and expectations when reading the prior art at the time of the invention." *Id*. at 1030. Such "reliance on [a patentee's statements] merely as confirmation of how a [skilled artisan] would understand . . . prior art, is not erroneous." *Id*.; *see also Pfizer*, 480 F.3d at 1365 (rejecting argument that a drug's effects were unexpected, where "there is a suggestion in [the patentee]'s supplemental filing with the FDA that it was known that the [drug] would work for its intended purpose"); *Thomas & Betts Corp. v. Litton Sys., Inc.*, 720 F.2d 1572,

1580-81 (Fed. Cir. 1983) (relying on "unpublished internal criteria" as evidence of state of the art).[8]

Second, Amarin argues that most of its statements are irrelevant "because they post-date the invention." Pls.' FFCL ¶ 753. But the statements were all about *prior art*, and the Federal Circuit has repeatedly "approved use of later publications as evidence of the state of art existing on the filing date." *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1344 (Fed. Cir. 2003).

Third, Amarin argues that these documents "state that the prior art does not concern severely hypertriglyceridemic patients." Pls.' FFCL ¶ 754. But all of Amarin's representations about the prior art were in the context of Vascepa's indication focusing exclusively on severe hypertriglyceridemia. There was no reason to cite the prior art unless Amarin believed it applied to those patients. *E.g.*, DX 1800 at 16 (investor presentation targeting "[p]atients with very high triglycerides (≥500 mg/dL)").

c. Amarin's teaching-away arguments are meritless.

Unable to dispute that Defendants' references clearly taught the claimed invention, Amarin argues that other prior-art disclosures taught away from it. But none of Amarin's prior art meets the strict legal standard: "A reference does not teach away if it does not 'criticize, discredit, or otherwise discourage' investigation into the invention claimed." *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) (alteration omitted) (reversing judgment of nonobviousness).

i. Rambjør and von Schacky did not teach away.

Despite Amarin's contemporaneous reliance on Mori and Kurabayashi, Amarin now tries to counter those references (and others that corroborated them) with Rambjør and von Schacky—never once cited by Amarin to FDA or investors. Pls.' FFCL ¶¶ 684-95; *see* Defs.' FFCL ¶¶ 301-13. But these references do not "criticize, discredit, or otherwise discourage" using purified EPA to treat patients with severe hypertriglyceridemia, as required to teach away. Only Rambjør even tested EPA and DHA, and it concluded that only "EPA produced significant decreases" in triglycerides, suggesting that DHA was not even effective. DX 1961 at 3. von Schacky merely summarized previous studies, without providing any new data, let alone criticizing or discrediting EPA. DX 1605.

[8] Amarin cites *Neptune Generics, LLC v. Eli Lilly & Co.*, 921 F.3d 1372 (Fed. Cir. 2019), but it does not hold otherwise. Pls.' FFCL ¶¶ 747-48. *Neptune* affirmed an agency decision under the deferential, substantial-evidence standard, while acknowledging that "a patent owner's own disclosures to the FDA may be considered in assessing the state of the prior art." 921 F.3d at 1377.

Even if either reference taught away (they did not), their "isolated prior art disclosures" were neither reliable nor representative of "the prior art as a whole, . . . [which] does not teach away." *Merck & Cie v. Gnosis S.P.A.*, 808 F.3d 829, 834 (Fed. Cir. 2015). Rambjør itself warned against drawing conclusions from its "underpowered" study, calling instead for "[f]urther studies . . . to clearly define individual effects of EPA and DHA." DX 1961 at 4, 6. Mori also criticized Rambjør because it "had only a small number of subjects in the DHA group, was short in duration, and included only a 2-w[ee]k washout period between treatments." DX 1538 at 5, 9. Even if the two studies were equally reliable, a skilled artisan would have viewed Mori as more instructive on the expected effects of pure EPA: Mori tested a high purity of 96% (DX 1538 at 2), whereas Rambjør tested a lower purity of 91%, which would include more DHA or other impurities. DX 1961 at 3; Toth Tr. 1841:11-24.

As to von Schacky, Dr. Toth conceded that it only provided one author's "interpretation," whereas a skilled artisan "would look at the underlying clinical studies" herself. Toth Tr. 1847:25-1848:8. Even if a skilled artisan considered von Schacky, she would view it as unreliable and internally inconsistent: von Schacky wrongly reported that "no effects of either EPA or DHA were seen on LDL levels" in Mori (DX 1605 at 5), which is "not what Mori said." Toth Tr. 1847:8-17.

ii. Alleged advantages of DHA did not teach away.

Amarin also argues that the prior art "taught away from using high purity EPA in patients with severe hypertriglyceridemia, as [Mori] disclosed that only EPA increased fasting glucose," while DHA had other benefits. Pls.' FFCL ¶¶ 673-80. This argument is baseless. Defs.' FFCL ¶¶ 785-91. Neither Mori nor any other studies "criticize, discredit, or otherwise discourage" using EPA. *Galderma*, 737 F.3d at 739. Even if DHA were preferred, "[a] reference does not teach away . . . if it merely expresses a general preference for an alternative invention." *Id.* at 738. In other words, "the teaching away inquiry does not focus on whether a person of ordinary skill in the art would have merely *favored* one disclosed option over another." *Bayer Pharma AG v. Watson Labs., Inc.*, 874 F.3d 1316, 1327 (Fed. Cir. 2017). Where, as here, the prior art disclosed two options—e.g., EPA and DHA—"the fact that there may be reasons a skilled artisan would prefer one over the other does not amount to a teaching away from the lesser preferred but still workable option." *Id.*

Put differently, whether DHA had other advantages did not diminish the motivation to use

EPA to reduce triglycerides without raising LDL-C. Federal Circuit precedent "does not require that the motivation be the *best* option, only that it be a *suitable* option." *Par Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1197-98 (Fed. Cir. 2014). And "the legally proper question is whether [EPA] would be a suitable option in some respects, not necessarily in every respect." *E.I. du Pont De Nemours & Co. v. MacDermid Printing Sols., LLC*, 657 F. App'x 1004, 1014 (Fed. Cir. 2016).

If DHA were truly preferred over EPA, the drug industry would have developed pure DHA. But as Dr. Toth admitted, DHA "was just used investigationally" and never commercialized to reduce triglycerides or cardiovascular risk. Toth Tr. 1904:7-11. By contrast, pure EPA was marketed in Japan to reduce triglycerides, used on a large scale to reduce cardiovascular risk in JELIS, and even given to patients with severe hypertriglyceridemia. Toth Tr. 1904:4-6, 1903:5-7, 1862:23-1863:1.

Despite Epadel—a real-world, pure EPA product—Amarin argues that pure EPA was not obvious because GSK "developed the Lovaza omega-3 mixture in 2004 . . . rather than high purity EPA." Pls.' FFCL ¶ 725. But while Lovaza was *launched* in 2004, it was *developed* earlier—testing on the product (originally called Omacor) was first reported in the 1997 Harris paper, which was *before* Mori taught that DHA caused the increase in LDL-C. DX 1531 at 1; Pls.' FFCL ¶ 788. Once Lovaza was made, GSK had no reason to develop pure EPA, which would only cannibalize its own sales. Regardless, "mere passage of time without the claimed invention is not evidence of non-obviousness." *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1325 (Fed. Cir. 2004).

iii. Data on Lovaza, fibrates, and niacin did not teach away.

Amarin also cites data for Lovaza, fibrates, and niacin as purported evidence that EPA would increase LDL-C in patients with severe hypertriglyceridemia. Pls.' FFCL ¶¶ 706-15. In particular, Amarin cites evidence that these drugs increased LDL-C in patients with mean triglycerides of 726 and 816 mg/dL. PDX 6-7; PDX 6-8. But none of Amarin's references criticize, discredit, or discourage using EPA in a patient with triglycerides of 500 mg/dL. Defs.' FFCL ¶¶ 751-64.

First, a skilled artisan would not have relied on data regarding Lovaza, a mixture of EPA and DHA, to predict the effects of EPA alone. As Dr. Toth admitted, EPA and DHA "clearly had some different effects," so "the fact that Lovaza itself has an LDL-C side effect doesn't answer the question of whether that side effect could be attributed to solely EPA." Toth Tr. 1829:6-8, 1801:21-25.

Second, the effects of fibrates and Lovaza in patients with triglycerides far above 500 mg/dL (726 and 816 mg/dL) does not address the relevant question, which is whether there was a reasonable expectation of success at *any* triglyceride level of 500 mg/dL or more. Again, "claims which are broad enough to read on obvious subject matter are unpatentable even though they also read on nonobvious subject matter." *In re Cuozzo*, 793 F.3d at 1281. Here, all claims "are broad enough" to cover patients with triglycerides of exactly 500 mg/dL. Thus, even if EPA's LDL-C effects were unexpected in patients with triglycerides above 700 mg/dL, that would not avoid obviousness. If anything, the fibrates data suggested that LDL-C would *not* increase: There was no significant increase in patients with triglycerides of 432 mg/dL, which is closer to 500 than 726. PDX 6-7.

Third, in any event, a skilled artisan would not expect pure EPA to have the same effects as fibrates or niacin. At trial, Amarin "did not cite . . . any prior art comparing the LDL-C effects of niacin or fibrates on the one hand with pure EPA." Toth Tr. 1804:17-20. In fact, Amarin's 2008 submission to FDA suggested the opposite: "The mechanisms with which TG lowering therapies such as fibrates or niacin exert their effects are fairly well established; however, a mechanism to explain the hypotriglyceridemic effects of omega-3 fatty acids has not been clarified." DX 1816 at 9-10. Likewise, "the examiner rejected Amarin's argument that a skilled artisan would extrapolate the results observed with a fibrate to omega-3 fatty acids like pure EPA" (Toth Tr. 1804:2-6) because fibrates are "structurally and biologically very different from EPA-E." DX 1587 at 19.

Fourth, even if it were proper to compare EPA to other drugs, the notion that all triglyceride-lowering drugs increased LDL-C in patients with severe hypertriglyceridemia is false. The 2007 label for Lipitor reported reductions in both triglycerides *and* LDL-C in a clinical trial in which the "median (min, max) baseline TG level was 565 (267-1502)"—i.e., a median of 565 mg/dL, with a range of up to 1502 mg/dL. DX 1986 (current label) at 21; DX 3007 (2007 label) at 11-12. Thus, the Lipitor label proves that drugs in the prior art could, in fact, reduce triglycerides without increasing LDL-C in patients with severe hypertriglyceridemia. Toth Tr. 1815:6-1817:8.[9]

[9] Citing *Eaton Corp. v. Appliance Valves Corp.*, 790 F.2d 874 (Fed. Cir. 1986), Amarin argues that Defendants' reliance on the Lipitor label is "procedurally improper" because it was not on their pre-trial section 282 notice. Pls.' FFCL ¶¶ 735-38. But Amarin ignores the holding in *Eaton*, which *allowed* unlisted prior art, because "section 282 does not dictate an arbitrary or absolute rule barring

3. No secondary considerations weigh against obviousness.

Amarin also failed to produce evidence of any relevant secondary considerations. Regardless, Defendants' "strong showing of obviousness [would] stand even in the face of considerable evidence of secondary considerations." *ZUP, LLC v. Nash Mfg., Inc.*, 896 F.3d 1365, 1374 (Fed. Cir. 2018).

a. The lack of LDL-C increases does not support the asserted claims.

Amarin argues that EPA's lack of increase in LDL-C was unexpected, met a long-felt need, overcame skepticism, and has been praised. Pls.' FFCL ¶¶ 768, 797, 809, 817. Amarin is wrong.

First, the fact that EPA is neutral as to LDL-C was not "unexpected"—it was reasonably expected based on Mori and other prior art. Defs.' FFCL ¶¶ 301-13, 819-22. The reduction in Apo B was equally expected. *Id.* ¶¶ 891-94. Even if these results were unexpected in patients with triglycerides *far above* 500 mg/dL, any such "showing of unexpected results is not commensurate in scope with the degree of protection sought by the claimed subject matter," which also includes triglycerides of *exactly* 500 mg/dL. *In re Harris*, 409 F.3d 1339, 1344 (Fed. Cir. 2005).

Second, any "need" to avoid raising LDL-C is irrelevant because "others had previously solved the long-felt need." *In re PepperBall Techs., Inc.*, 469 F. App'x 878, 882 (Fed. Cir. 2012); Defs.' FFCL ¶¶ 809-18. Even apart from Epadel, Dr. Toth agreed that "if a patient is experiencing LDL-C increases because of Lovaza, a statin could be added" to avoid it. Toth Tr. 1874:16-19; *see*

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introduction of relevant, material evidence on the purely formalistic fact that notice of reliance was lacking." 790 F.2d at 879-80. The statute only warrants excluding evidence when "a party has been deprived of an adequate opportunity to present its case," which is not the case where a plaintiff "knew or should have known" of the disputed art, and its expert "was given sufficient time to read and review it" at trial. *Id.* Likewise, here, Dr. Toth was "familiar with LIPITOR," had "prescribed i[t] thousands of times," and agreed that "a skilled artisan by March 2008 would be very familiar with the LIPITOR label." Toth Tr. 1808:2-13. Amarin also admits that "Defendants had identified the current, 2019 Lipitor label," which includes the same clinical data. Pls.' FFCL ¶ 738; DX 1986 at 21. Nor did Defendants introduce the 2007 label as affirmative evidence of obviousness, but only to impeach Dr. Toth's opinion that all other drugs at the time raised LDL-C. Toth Tr. 1809:25-1813:1.

Defendants also did not engage in any "sudden switch on the last day of trial" on the issue of whether statins like Lipitor are triglyceride-lowering drugs. Pls.' FFCL ¶ 738. Consistent with Dr. Heinecke's expert reports—and with no objection from Amarin's counsel—Dr. Heinecke repeatedly testified on the third day of trial that statins reduce triglycerides in patients with severe hypertriglyceridemia without raising LDL-C. Heinecke Tr. 853:4-10, 873:4-6, 910:13-17.

DX 1953 (Amarin's validity contentions) at 18. There was thus no "need" to avoid raising LDL-C.[10]

Third, Amarin presented no expert testimony at trial on any skepticism that EPA would be neutral as to LDL-C. Amarin cites none, and Dr. Toth did not include skepticism in his objective indicia for LDL-C. PDX 6-24. Regardless, Amarin cites only *two* alleged skeptics on an Amarin-sponsored panel, which is hardly representative of the industry. Pls.' FFCL ¶ 808. Moreover, any skepticism by these individuals is irrelevant because there is no evidence that they "were previously aware of the prior art references" that Defendants have cited. *PharmaStem*, 491 F.3d at 1365.

Fourth, there is no evidence that Vascepa has been "praised" for avoiding LDL-C increases. Defs.' FFCL ¶¶ 823-28. Amarin cites articles by Castaldo and Fialkow, but these simply note the *fact* that Vascepa does not raise LDL-C based on MARINE. Pls.' FFCL ¶¶ 813-14. Amarin also cites O'Riordan (*id*. ¶ 816), but ignores statements that minimize Vascepa's benefits because the typical LDL-C increases from Lovaza were "'modest' and 'not that big an issue,'" especially since Lovaza "works well with statin therapy." DX 1581 at 2. That is not "praise" for Vascepa.

b. REDUCE-IT does not support the asserted claims.

Amarin also relies on REDUCE-IT as alleged evidence of unexpected results, long-felt need, skepticism, and praise. Pls.' FFCL ¶¶ 768, 797, 809, 817. But REDUCE-IT is irrelevant to this case.

i. REDUCE-IT lacks a nexus to the asserted claims.

Amarin admits "[t]here must be a nexus between the merits of the claimed invention and the objective indicia of non-obviousness." *Id*. ¶ 521. There is no nexus here. Defs.' FFCL ¶¶ 830-53.

As an initial matter, there is no "rebuttable presumption of nexus" here. Pls.' FFCL ¶ 775. A "patentee [i]s not entitled to a presumption of nexus [where] the product embodie[s] at least two patented inventions." *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1375 (Fed. Cir. 2019). That is undisputed here: "Amarin has separate patents covering the method used in the REDUCE-IT study," and "those patents are not being asserted." Toth Tr. 1895:4-10. Amarin represented that

[10] The fact that statins could be used with Lovaza to meet any long-felt need does not "negate Defendants' entire obviousness case." Pls.' FFCL ¶ 795. Amarin admits in the very next paragraph that a skilled artisan "would not have found it desirable to use two different pills"—i.e., Lovaza and a statin. *Id*. ¶ 796. As Dr. Toth admitted, "a skilled artisan would have been motivated to develop a single pill that treats severe hypertriglyceridemia without LDL-C increases." Toth Tr. 1822:12-21.

Vascepa embodies those unasserted patents by listing them in FDA's Orange Book. DX 2299; 21 C.F.R. § 314.53(b). "This is not a situation where the success of a product can be attributed to a single patent," so "there is no presumption that the product's success was due only to the [asserted] patent[s]." *Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1289, 1299 (Fed. Cir. 2010).

Regardless of any presumption, REDUCE-IT lacks a nexus to the claims for multiple reasons:

- All claims require baseline triglycerides of at least 500 mg/dL, but "REDUCE-IT focused on patients with triglycerides *below* 500." Toth Tr. 1894:12-14 (emphasis added).
- Whereas "*all* the patients in REDUCE-IT were taking statins," "*none* [of] the asserted claims require a statin"—some even exclude it. Toth Tr. 1896:15-24 (emphasis added). Thus, all asserted claims cover the patients in MARINE, 75% of whom were *not* on statins. Pls.' FFCL ¶ 353. REDUCE-IT provides no evidence of any benefits for those patients.
- All the claims cover the use of EPA for only 12 weeks (e.g., MARINE), yet Dr. Toth "didn't offer any opinion that REDUCE-IT showed any cardiovascular benefit . . . as of 12 weeks." Toth Tr. 1895:14-19. On the contrary, he agreed that "if you stop [Vascepa] at four months, then you're going to lose that benefit." Toth Tr. 1896:6-14.
- All the claims are directed to a method of reducing triglycerides, yet the REDUCE-IT investigators found that the reported cardiovascular benefits "occur irrespective of the attained triglyceride level"—that is, they "may be explained by metabolic effects *other than* a reduction of triglyceride levels." DX 1641 (Bhatt) at 10 (emphasis added).
- Most claims require no increase in LDL-C (i.e., Amarin's alleged invention), yet REDUCE-IT saw "no substantial difference in the benefit" of EPA "according to whether the patients . . . had an increase in LDL cholesterol levels." DX 1641 (Bhatt) at 7.
- REDUCE-IT was limited to patients who "had established cardiovascular disease or . . . diabetes mellitus and at least one additional risk factor." DX 1641 (Bhatt) at 2. By contrast, "aside from severe high triglycerides, there's no other risk factors required by the patents related to cardiovascular issues" in the MARINE study. Toth Tr. 1894:22-25.

Each of these reasons is fatal to any nexus. Because REDUCE-IT is "not commensurate with the full scope of the patent's claims," *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 965 (Fed. Cir. 2014), and "actually result[ed] from something other than what is [ ] claimed . . . , there is no nexus to the merits of the claimed invention." *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

ii. REDUCE-IT merely confirmed the results of JELIS.

Even apart from the lack of nexus, Amarin's alleged secondary considerations fall flat in view of JELIS, which showed that Epadel reduces cardiovascular risk years before REDUCE-IT. Defs.' FFCL ¶¶ 854-90. Amarin now argues that JELIS had "significant design flaws" (Pls.' FFCL ¶ 770), but its litigation-inspired arguments are directly contrary to its previous representations to FDA:

> [O]verall, JELIS was a very large, well-designed study with blinded endpoint evaluation that demonstrated a statistically significant reduction in CV risk due to a statin add-on therapy; Amarin believes that its results should not be dismissed lightly. . . . These points strongly support the consideration of JELIS study results in evaluating the potential CV benefits of Vascepa therapy.

DX 1836 at 71, 81. Likewise, Dr. Toth "personally ha[s] praised the JELIS trial" (Toth Tr. 1912:1-6), calling it "a nice Japanese study" that showed "a whopping 53% reduction in risk." DX 1709 at 16-17. As Drs. Ketchum and Toth admitted, such statements were "truthful and accurate," and did not "overstate[] the results of the JELIS study." Ketchum Tr. 232:15-18; Toth Tr. 1909:6-13.

Even apart from these pre-suit statements, Amarin's criticisms are not credible. JELIS was a five-year study in more than 18,000 patients, which showed a statistically significant, "19% relative reduction in major coronary events" and concluded that "EPA is a promising treatment for prevention of major coronary events." DX 1553 (Yokoyama 2007) at 1. These results were published in *The Lancet*, "a top medical journal" with "a very strong reputation in the medical community" and "rigorous" peer review. Toth Tr. 1899:20-1900:8. In patients with hypertriglyceridemia, the results were even more dramatic: "suppression of the cardiovascular event occurrence . . . was 53%." DX 1524 (WO '118) at 45-46; Toth Tr. 1923:1-1924:13. REDUCE-IT merely confirmed that result.[11]

c. Vascepa is not a relevant commercial success.

Vascepa has not turned a profit, has garnered only a small market share, and at least 75% of prescriptions are for patients with triglycerides *below* 500 mg/dL, which are outside the scope of the claims and have no nexus to the claimed invention. Defs.' FFCL ¶¶ 435-47, 895-905.

C. The three claims that exclude concurrent lipid altering therapy are not infringed, and the remaining seven claims (which allow statins) were at least obvious to try.

As a third, independent basis to rule for Defendants, Amarin failed to prove that Defendants infringe the three claims that exclude concurrent lipid altering therapy ('728 claims 1 and 16, and '715 claim 14), and the seven other claims are invalid because they are broad enough to cover the obvious use of a statin to achieve the claimed LDL-C and Apo B effects. Defs.' FFCL ¶¶ 907-29.

[11] The fact that FDA did not accept JELIS, but later accepted REDUCE-IT, is irrelevant. FDA applies a far more rigorous standard than the "reasonable expectation of success" required by patent law, and thus difficulties in receiving FDA approval "are not particularly probative with respect to obviousness." *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013).

Noninfringement: In an attempt to meet its burden, Amarin argues that the indication does "not requir[e] concurrent lipid altering therapy," and thus "it is within the scope of the approved indication to administer VASCEPA to someone not" on such therapy. Pls.' FFCL ¶¶ 346-47. But that is irrelevant. Although the scope of FDA approval "includes" using EPA as monotherapy, "it also includes" using EPA with other drugs, so monotherapy is "not *specifically* encourage[d]" over combination therapy. *Grunenthal*, 919 F.3d at 1339 (emphasis added). As Dr. Budoff admitted, "nothing in the . . . label as a whole suggest[s] any preference for using icosapent with or without a statin," which is left "entirely up to the physician's discretion." Budoff Tr. 523:7-25.

Indeed, neither the indications and usage section nor the dosage and administration section mentions anything about concurrent lipid altering therapies, much less requires excluding them. The only statement that even relates to concurrent therapy is in the clinical studies section, which states that "[t]wenty-five percent of patients were on concomitant statin therapy." Pls.' FFCL ¶ 352. Amarin asserts that "[c]linicians appreciate . . . that the remaining 75% of patients in the study described in the Clinical Studies section were not on concurrent lipid altering therapy" (*id.* ¶ 353), but that is false. As Dr. Budoff admitted, "a statin is an *example* of a lipid-altering therapy," "[*b*]*ut there are other lipid-altering therapies*"—e.g., fibrates, niacin, and ezetimibe. Budoff Tr. 520:13-25 (emphasis added). Contrary to Amarin's theory, "the labeling doesn't say anything about whether this 75 percent of patients were taking a different lipid-altering therapy." Budoff Tr. 522:22-25.

Regardless, "[*m*]*erely describing* the infringing use . . . *will not suffice*"—labelling that "does not *require*" the described use "does not encourage infringement." *Horizon*, 940 F.3d at 702 (emphasis added). Here, it is undisputed that the labelling does not "require" monotherapy. As Dr. Budoff admitted, the statement that Amarin cites "is not an instruction to doctors to make sure they use a statin," and "it's not mandating *not* to use a statin either." Budoff Tr. 522:5-9 (emphasis added).

Obviousness: The seven remaining claims that do not exclude concurrent lipid altering therapy are all invalid—even under Amarin's theory that skilled artisans lacked a reasonable expectation of success with EPA alone. Defs.' FFCL ¶¶ 921-29. Dr. Toth repeatedly admitted that the combination of purified EPA with a statin (which is allowed by these claims and was known in the art) was reasonably expected to reduce triglycerides and Apo B without increasing LDL-C:

- "[B]y March 2008, it was known that EPA could be used with a statin"—e.g., "JELIS involved pure EPA with a statin," and "motivated a skilled artisan to run a similar type of study in the United States." Toth Tr. 1876:25-1877:2, 1878:24-1879:1, 1903:13-17.
- More specifically, "pure EPA was given to at least one patient [with triglycerides] above 500 with a statin," as shown in Nakamura. Toth Tr. 1878:16-23; DX 1539 at 1-2.
- Skilled artisans knew that "statins can reduce LDL-C and apo B." Toth Tr. 1876:13-15.
- "[A] skilled artisan would know . . . that taking 4 grams of Lovaza with a statin could prevent LDL-C increases in patients with very high triglycerides." Toth Tr. 1874:10-15.
- "So a skilled artisan, in 2008, would understand that if you give pure EPA with a statin," "you won't have as much of an LDL increase, or perhaps you won't increase LDL" at all. Toth Tr. 1879:16-20. Likewise, "a skilled artisan, in March 2008, would understand that if you give pure EPA with a statin, you're likely to have an apo B decrease." Toth Tr. 1879:21-25. Thus, it was "known in March 2008" that "pure EPA could be used with statins to reduce apo B and LDL-C." Toth Tr. 1881:1-5.
- Critically, a skilled artisan would have reasonably expected these results *regardless* of "whether the triglyceride level is 400 or 550." Toth Tr. 1880:1-3.
- That obvious method falls within the scope of the "claims that allow for the use of a statin[,] [which] would include using 4 grams pure icosapent with a statin to . . . not have an LDL-C increase," as well as "to reduce apo B." Toth Tr. 1886:15-24.

Proof of obviousness is thus undisputed, clear, and convincing. Amarin's arguments lack merit.

First, Amarin argues these concessions amount to a new argument and a new "combination of prior art references." Pls.' FFCL ¶ 727. Not so. The Lovaza PDR—one of Defendants' combination references—expressly discloses the administration of omega-3 fatty acids to patients with "simvastatin . . . to control their LDL-C." DX 1535 at 2. Moreover, Dr. Heinecke testified on direct that even if LDL-C increases were expected with the EPA dose disclosed in Mori, "statins were available [in the prior art] and could be used to lower LDL cholesterol in patients who had an increase in LDL cholesterol." Heinecke Tr. 808:23-809:1; *see also id*. at 809:21-810:10, 811:12-812:1.[12]

Regardless, Amarin did not object to any of the above testimony at trial. Amarin's post-trial objection is thus "waived by failing to object at trial." *Lucent Techs., Inc. v. Gateway, Inc.*, 580 F.3d 1301, 1325 (Fed. Cir. 2009); *see also Lifestyle Enter., Inc. v. United States*, 751 F.3d 1371, 1377

[12] Dr. Heinecke also testified that a patient in Nakamura with triglycerides above 500 mg/dL took pure EPA with a statin. Heinecke Tr. 733:6-734:3. While Nakamura was not one of his core references, Defendants are "rel[ying] on [Nakamura] not as part of a prior art combination, but only in rebutting [Amarin]'s assertion that there was no motivation to combine" the Lovaza PDR and Mori. *Persion Pharm. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184, 1193 (Fed. Cir. 2019).

(Fed. Cir. 2014) ("waiver can itself be waived by not being raised" (quotation omitted)).[13]

Second, Amarin argues that "Defendants have failed to show motivation to combine purified EPA and a statin" because Dr. Heinecke testified that it is "easier to take one pill" than two. Pls.' FFCL ¶¶ 728-29. But while a single pill was preferred, Dr. Heinecke made clear that statins were still an obvious way to "counteract" LDL-C increases. Heinecke Tr. 809:21-810:14. Moreover, even under Amarin's view that Mori showed a (nonsignificant) 3.5% LDL-C increase with EPA, this was still less than the (significant) 8% increase with DHA. DX 1538 at 3. Thus, it was at least obvious to use EPA to mitigate the increase in LDL-C, and then add a statin to avoid it. Heinecke Tr. 808:20-25. Because EPA was less likely to raise LDL-C, a skilled artisan would also prefer to use it in patients taking statins to avoid "negating their LDL-C lowering effects." Pls.' FFCL ¶ 789.

Even if a skilled artisan believed that pure EPA was no better than Lovaza, it would still be obvious to combine EPA with a statin, just as it was obvious to combine Lovaza with a statin. Motivation does not require an expected *improvement*. It is "sufficient to show" an expectation "that the new [invention] will have *similar properties* to the old." *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007) (quotation omitted; emphasis added).

In any event, there is no dispute that purified EPA actually *was* administered with a statin in the prior art, so Amarin cannot dispute that the combination was obvious. Toth Tr. 1876:25-1879:1, 1903:13-17; *see also Nalpropion Pharm., Inc. v. Actavis Labs. FL, Inc.*, 934 F.3d 1344, 1354-55 (Fed. Cir. 2019) (rejecting patentee's argument that it was not obvious to combine two drugs, where "[t]he inescapable, real-world fact here is that people of skill in the art *did combine*" them).

Third, Amarin asserts that the claims "require that the purified EPA itself not raise LDL-C," regardless of whether "that rise can be negated through some other agent." Pls.' FFCL ¶ 730. That is wrong. The claims recite a method "comprising" the use of EPA, which "indicates that the claim is open-ended and allows for additional steps"—e.g., adding a statin to achieve the claimed effects. *Medichem, S.A. v. Rolabo, S.L.*, 353 F.3d 928, 933 (Fed. Cir. 2003) (quotation omitted).

Fourth, while admitting that "statins 'could' prevent LDL-C increases in patients with severe

[13] Under Amarin's logic, its own argument that Section 2.1 of Defendants' labels induces infringement was also waived because it was not mentioned in Amarin's pre-trial filings.

hypertriglyceridemia," Amarin argues that this "depend[s] upon the 'magnitude of the elevation' and the 'baseline TG level.'" Pls.' FFCL ¶ 734. But whether the effects were unexpected in some patients is irrelevant. As long as the effects were obvious for at least *some* patients, the claims are invalid. *In re Cuozzo*, 793 F.3d at 1281 ("claims which are broad enough to read on obvious subject matter are unpatentable even though they also read on nonobvious subject matter" (quotation omitted)).

D. The nine asserted claims that require specific lipid effects are not infringed, and the remaining, broadest claim was at least obvious to try.

As a fourth, independent basis to grant judgment for Defendants, the nine asserted claims that require specific effects on a patient's lipids beyond a general reduction in triglycerides are not infringed, and the remaining claim that does not require such effects ('929 patent claim 1) is invalid.

Noninfringement: As the Court previously found, Amarin's "own clinical study explicitly establishes that some patients received the triglyceride reductions required by all Asserted Claims without getting the other health benefits required by the Other Health Benefits Claims—so at least some substantial non-infringing uses must exist." ECF No. 278 at 13 n.6. Thus, "induce[d] infringement cannot be inferred"—the labelling must "instruct" and "require" doctors to administer Defendants' products with the intent to achieve the claimed effects. *Horizon*, 940 F.3d at 702.

Amarin has failed to make that showing. Defs.' FFCL ¶¶ 932-52. As Amarin admits, "[t]he plain language" of the indication only "encourages clinicians to administer VASCEPA to reduce TGs in severely hypertriglyceridemic patients"—it says nothing about any minimum reduction, or anything about LDL-C or Apo B. Pls.' FFCL ¶ 323; Budoff Tr. 513:3-5, 519:23-25.

Only the clinical studies section even mentions these effects. But as Dr. Budoff admitted, this section merely "report[s] on observations concerning the clinical trial that's being reported in [the] table"—"*these are not instructions* on how to use icosapent." Budoff Tr. 511:9-15 (emphasis added). At most, the clinical studies section "[m]erely describ[es]" that the claimed effects occurred in *some* patients (but not in others). *Horizon*, 940 F.3d at 702; *see* Budoff Tr. 512:6-9, 514:20-515:8.

Amarin also relies on the Warnings and Precautions section, which according to Amarin "omits any warning that patients' LDL-C levels may rise." Pls.' FFCL ¶ 329. But Amarin does not contend that such silence is an instruction. Instead, Amarin argues that "[t]he absence of a warning

would be conspicuous to clinicians because the prescribing information for Lovaza and several fibrates contain such a warning." *Id*. ¶ 330. This theory, however, impermissibly "asks [the Court] to look outside the label to understand the alleged implicit encouragement in the label." *Takeda*, 785 F.3d at 634. "Defendants' labels never tell doctors to compare the icosapent clinical trial to the Lovaza clinical trial," or even "refer to the Lovaza label at all." Budoff Tr. 516:22-517:2. If anything, the labels "warn[] [doctors] *against* comparing adverse reactions from two clinical trials involving 2 different drugs." Budoff Tr. 517:16-19 (emphasis added; citing DX 2256 at 3, § 6.1).

Without that comparison, Amarin's theory of infringement for the LDL-C claims fails. Dr. Budoff admitted that the "LDL-C statement in [the] label would carry significance to a doctor *only because and if* the doctor understood that Lovaza had this side effect"—otherwise, "it wouldn't mean much to the doctor to say there was no LDL-C increase." Budoff Tr. 516:15-21 (emphasis added).

As for the claimed reduction in Apo B, Dr. Budoff admitted that it "is not an intended result with regard to treating severe hypertriglyceridemia." Budoff Tr. 519:19-22. Indeed, Amarin sought a *separate* indication "to reduce . . . Apo B," which FDA rejected. DX 1558 at 1. Dr. Budoff himself "do[es]n't often measure" Apo B (Budoff Tr. 519:14-18), and Dr. Sheinberg emphasized that the reduction reported in the clinical studies section "is absolutely not clinically significant," so using EPA to reduce Apo B would be "a breach of the standard of care." Sheinberg Tr. 643:16-25.

Obviousness: The sole remaining claim—'929 patent claim 1—does not exclude an increase in LDL-C, and does not require a reduction in Apo B, so it was at least obvious to try regardless of whether those results were expected. Defs.' FFCL ¶¶ 953-56. As a matter of law, a skilled artisan "need only have a reasonable expectation of success of developing the *claimed* invention," *Allergan*, 726 F.3d at 1292 (emphasis added), which here only requires "reducing triglycerides." This result was undisputedly obvious: Dr. Toth admitted that "a skilled artisan, as of March 2008, would have reasonably expected purified EPA to reduce triglyceride levels above 500." Toth Tr. 1860:12-15.[14]

III. CONCLUSION

Amarin failed to prove infringement of any asserted claim, and all asserted claims are invalid.

[14] Any alleged unexpected results on LDL-C and Apo B are "not commensurate with the full scope of" this claim, which includes patients who do not receive these benefits. *Allergan*, 754 F.3d at 965.

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/s/ Claire Fundakowski
W. West Allen (Nev. Bar No. 5566)
HOWARD & HOWARD ATTORNEYS PLLC
3800 Howard Hughes Parkway, Suite 1000
Las Vegas, NV 89169
Tel: (702) 257-1483
Email: wwa@h2law.com

Charles B. Klein (admitted *pro hac vice*)
Claire A. Fundakowski (admitted *pro hac vice*)
WINSTON & STRAWN LLP
1700 K Street NW
Washington, DC 20006
Tel: (202) 282-5000
Email: cklein@winston.com,
cfundakowski@winston.com

George C. Lombardi (admitted *pro hac vice*)
Alison A. Heydorn (admitted *pro hac vice*)
WINSTON & STRAWN LLP
35 W. Wacker Drive
Chicago, IL 60601
Tel: (312) 558-5969
Email: glombard@winston.com
aheydorn@winston.com

Eimeric Reig-Plessis (admitted *pro hac vice*)
WINSTON & STRAWN LLP
101 California Street
San Francisco, CA 94111
Tel: (415) 591-6808
Email: ereigplessis@winston.com

Attorneys for Defendants Hikma Pharmaceuticals USA Inc. and Hikma Pharmaceuticals International Limited

/s/ Caroline Sun
Michael D. Rounds (Nev. Bar No. 4734)
Ryan J. Cudnik (Nev. Bar No. 12948)
BROWNSTEIN HYATT FARBER SCHRECK, LLP
5371 Kietzke Lane
Reno, NV 89511
Tel.: (775) 324-4100 / Fax: (775) 333-8171
Email: mrounds@bhfs.com,
rcudnik@bhfs.com

Constance S. Huttner (admitted *pro hac vice*)
Frank D. Rodriguez (admitted *pro hac vice*)
James Barabas (admitted *pro hac vice*)
Caroline Sun (admitted *pro hac vice*)
Beth Finkelstein (admitted *pro hac vice*)
WINDELS MARX LANE & MITTENDORF, LLP
1 Giralda Farms, Suite 100
Madison, NJ 07940
Tel: (973) 966-3200 / Fax: (973) 966-3250
Email: chuttner@windelsmarx.com,
frodriguez@windelsmarx.com
jbarabas@windelsmarx.com,
csun@windelsmarx.com,
bfinkelstein@windelsmarx.com

Attorneys for Defendants Dr. Reddy's Laboratories, Inc. and Dr. Reddy's Laboratories, Ltd.

CERTIFICATE OF SERVICE

Pursuant to Federal Rule of Civil Procedure 5(b) and Section IV of the District of Nevada Electronic Filing Procedures, I hereby certify that I am an employee of WINSTON & STRAWN LLP, and on this 28th day of February, 2020, I served the document entitled, **DEFENDANTS' POST-TRIAL BRIEF**, on all counsel of record through the CM/ECF system.

/s/ Alison M. Heydorn
Employee of Winston & Strawn LLP